


ORIGINAL RESEARCH

Childhood Blood Pressure, Carotid Intima Media Thickness, and Distensibility After In Utero Exposure to Gestational Hypertensive Disorders

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BACKGROUND: Offspring exposed to gestational hypertensive disorders have higher blood pressure and increased risk of stroke in later life. Gestational hypertensive disorders might influence vascular development in the offspring, predisposing them to a higher blood pressure and stroke in later life.

METHODS AND RESULTS: In a population-based cohort among 4777 mother–offspring pairs, we examined whether gestational hypertension, preeclampsia, and higher gestational blood pressure across the full blood pressure spectrum were associated with offspring blood pressure, carotid intima media thickness, and distensibility at the age of 10 years. Offspring exposed to gestational hypertension, but not preeclampsia, had higher systolic and diastolic blood pressure (0.17 [95% CI, 0.02–0.31] and 0.23 [95% CI, 0.08–0.38] increases in standard deviation scores, respectively), whereas no associations with intima media thickness and distensibility were present. Higher maternal systolic and diastolic blood pressure in early, mid, and late pregnancy were associated with higher offspring systolic and diastolic blood pressure and lower distensibility (P values <0.05), but not with intima media thickness. The associations were not explained by maternal, birth, or child factors. Paternal systolic and diastolic blood pressure were also associated with these offspring outcomes (P values <0.05), with a comparable strength as maternal–offspring associations.

CONCLUSIONS: Gestational hypertension and higher gestational blood pressure, even below the diagnostic threshold for gestational hypertensive disorders, are associated with higher offspring blood pressure and lower carotid distensibility. No associations were found for preeclampsia with offspring vascular outcomes. As maternal–offspring and paternal–offspring associations were comparable, these associations are more likely driven by genetic predisposition and shared lifestyle rather than by a direct intrauterine effect.

Key Words: blood pressure ■ carotid distensibility ■ carotid intima media thickness ■ gestational hypertensive disorders ■ offspring

Gestational hypertensive disorders occur in $\approx 5\%$ to 10% of pregnancies and are associated with adverse long-term cardiovascular outcomes in both mothers and offspring. Offspring of pregnancies affected by gestational hypertensive disorders seem to have a ≈ 2 mm Hg increased systolic blood pressure (SBP) and ≈ 1 mm Hg increased diastolic blood

pressure (DBP) during childhood and adolescence.^{1–3} One follow-up study among 6410 patients exposed to maternal preeclampsia or gestational hypertension showed a nearly 2-fold increased risk of stroke in adulthood.⁴ The clinical manifestations of gestational hypertensive disorders are at the extreme end of the blood pressure spectrum during pregnancy. Already small

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CLINICAL PERSPECTIVE

What Is New?

- Maternal gestational hypertension and higher maternal blood pressure throughout pregnancy were associated with higher childhood systolic and diastolic blood pressure and lower carotid distensibility; no associations with carotid intima media thickness were present.
- No associations of preeclampsia with offspring blood pressure, carotid intima media thickness, or distensibility were present.
- Associations of maternal gestational hypertension and blood pressure with offspring vascular outcomes were not explained by maternal, birth, or childhood factors; however, paternal blood pressure was associated with offspring vascular outcomes, with a comparable strength with maternal–offspring associations.

What Are the Clinical Implications?

- Maternal gestational hypertension and higher blood pressure throughout pregnancy are associated with a higher childhood blood pressure and lower carotid distensibility, which suggests increased arterial stiffness in the offspring from childhood onward.
- These associations are most likely driven by shared genetic predisposition and lifestyle factors between mothers and offspring rather than a direct intrauterine effect.
- Maternal gestational blood pressure profile might be useful for early identification of offspring at increased risk of an adverse cardiovascular risk profile in later life who may benefit from prevention strategies focused on reducing cardiovascular risk factors from early life onward.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
IMT	intima media thickness
SBP	systolic blood pressure
SDS	standard deviation score

increases across the full blood pressure spectrum, even below the clinical cutoff value of 140/90 mm Hg for the diagnosis of gestational hypertensive disorders, may influence offspring cardiovascular outcomes.^{5–7} Previous studies have shown that a higher gestational blood pressure across the full blood pressure spectrum is associated with higher blood pressure levels and an increased risk of hypertension in the offspring.⁵

The mechanisms underlying these associations remain to be elucidated. Gestational hypertensive disorders and already a higher maternal blood pressure during pregnancy may lead to an adverse intrauterine environment that initiates fetal developmental adaptations, leading to a suboptimal cardiovascular risk profile in later life. Animal studies suggest that uterine perfusion abnormalities, an intrauterine systemic hypoxic state, and increased antiangiogenic factors, features present in the development of gestational hypertensive disorders, lead to fetal vascular remodeling.⁸ This could lead to early development of atherosclerosis and predispose offspring to hypertension and increased risk of stroke in later life.⁸ In these animal models, offspring alterations in vascular structure and blood pressure predominantly occurred if these adverse circumstances were already present from early to mid pregnancy.⁸ However, the development of an early atherosclerotic phenotype in the offspring of affected pregnancies could also reflect shared genetic predisposition or lifestyle factors in mother–offspring pairs, especially because the mother herself also has an increased risk of cardiovascular diseases in later life after gestational hypertension or preeclampsia. Thus far, only a few studies investigated the associations of gestational hypertensive disorders with atherosclerotic changes in the offspring in human populations, which can be evaluated noninvasively by measurement of the carotid intima media thickness (IMT) and distensibility, and reported inconsistent findings.^{2,9–12}

We hypothesized that gestational hypertensive disorders and higher gestational blood pressure, already within the normal and prehypertension range, adversely influence vascular development in the offspring, which predisposes them to a higher blood pressure in later life. In a population-based prospective cohort study among 4777 mother–offspring pairs, we examined the associations of gestational hypertensive disorder status with offspring blood pressure, carotid IMT, and distensibility at the age of 10 years. Next, we further examined the associations of maternal gestational blood pressure on the full continuous scale with offspring blood pressure, carotid IMT, and distensibility independent of gestational hypertensive disorder status. We further explored whether critical periods for the associations of maternal gestational blood pressure with these offspring outcomes were present. Lastly, to obtain further insight into potential underlying mechanisms, we examined whether these associations were explained by maternal, birth, or child factors. We also compared the strength of the associations of maternal blood pressure and paternal blood pressure with these offspring outcomes, as a stronger

maternal–offspring association would support a direct intrauterine mechanism.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and Study Population

This study was embedded in the Generation R Study, a population-based prospective cohort from early pregnancy onward in Rotterdam, The Netherlands.¹³ All participants gave written informed consent. The study complies with the Declaration of Helsinki and was approved by the local MEC 198.782/2001/31. In total, 8879 women were enrolled during pregnancy. We excluded women with missing data on exposures ($n=5$), preexistent hypertension ($n=141$), and nonsingleton, nonlive births ($n=201$). Of the 5081 children who participated in the general follow-up visit at a median of 10 years, 286 did not have any outcome data available and another 18 children were excluded as a result of cardiac abnormalities. The total population for analysis consisted of 4777 mother–offspring pairs. Blood pressure measurements were available for 4745 children. Ultrasonographic measurements of carotid IMT and carotid distensibility were available for 4403 and 4225 children, respectively (Figure 1).

Parental Blood Pressure and Gestational Hypertensive Disorders

Maternal blood pressure was measured in early, mid, and late pregnancy (median [95% range]: 13.2 [9.6–17.5], 20.4 [18.5–23.6], 30.2 [28.4–32.9] weeks gestation, respectively), as described previously.¹⁴ Of the 4771 women, 3532 women had 3 blood pressure measurements, 1044 women had 2 blood pressure measurements, and 195 women had 1 blood pressure measurement during the course of pregnancy. Paternal blood pressure was measured at study enrollment. An Omron 907 automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe BV, Hoofddorp, The Netherlands) was used for the maternal and paternal blood pressure measurements while the participant was seated in upright position after a minimum 5-minute rest.¹⁵ The mean of 2 measurements with a 60-second interval was used for further analysis. We constructed standard deviation scores (SDSs) of maternal and paternal blood pressures to assess the associations of maternal and paternal blood pressures on the full continuous scale with offspring vascular outcomes.

Information on clinically diagnosed gestational hypertensive disorders was obtained from medical records that were cross-checked with the original

hospital charts.¹⁶ The clinical definition of gestational hypertension was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg after 20 weeks of gestation in previously normotensive women. Preeclampsia was defined as gestational hypertension with the addition of proteinuria.¹⁷ A normotensive pregnancy was defined as SBP < 140 mm Hg and DBP < 90 mm Hg throughout the entire course of pregnancy.

Childhood Blood Pressure, Carotid IMT, and Distensibility

Children were invited to our research center at the median age of 9.7 years (95% range, 9.4–10.7 years). SBP and DBP were measured with the child supine position. We measured blood pressure 4 times at the right brachial artery with a 1-minute interval using an automated sphygmomanometer Datascope Accutorr Plus (Paramus, NJ).¹⁸ The mean SBP and DBP were calculated using the last 3 measurements.

To make ultrasonographic recordings of the common carotid artery for the carotid IMT and distensibility measurements, we used the Logiq E9 (GE Medical Systems, Wauwatosa, WI). Children were in the supine position with the head tilted in the contralateral direction. The common carotid artery was identified in a longitudinal plane, ≈ 10 mm proximal from the carotid bifurcation. We obtained 3 recordings on both sides that included the coinciding cardiac cycles. Measurements were performed offline in a semiautomatic manner using Carotid Studio (Cardiovascular Suite; Quipu srl, Pisa, Italy).¹⁹ The recording was frozen on each R-wave of the ECG, the carotid IMT was then measured at the far wall as the average distance between the lumen–intima and the media–adventitia interfaces, and the average of all frames was computed. Carotid distensibility was defined as the relative change in lumen area during systole for a given pressure change. The lumen diameter was automatically computed as the average distance between the far and near media–adventitia interfaces for each frame of the acquired image sequence. The distension was calculated as the difference between the diastolic and systolic lumen diameter for each cardiac cycle in the recording. The average distension and diameter were used to calculate the distensibility. In a reproducibility study performed among 47 participants, the interobserver and intraobserver intraclass correlation coefficients were > 0.85 for distensibility and > 0.94 for IMT. We included all children with at least 1 successful carotid IMT or distensibility measurement, and the mean values were used for further analyses. We calculated the overall mean carotid IMT (mm) and distensibility ($\text{kPa}^{-1} \times 10^{-3}$). For the final analyses, distensibility was log-transformed to deal with a skewed distribution.

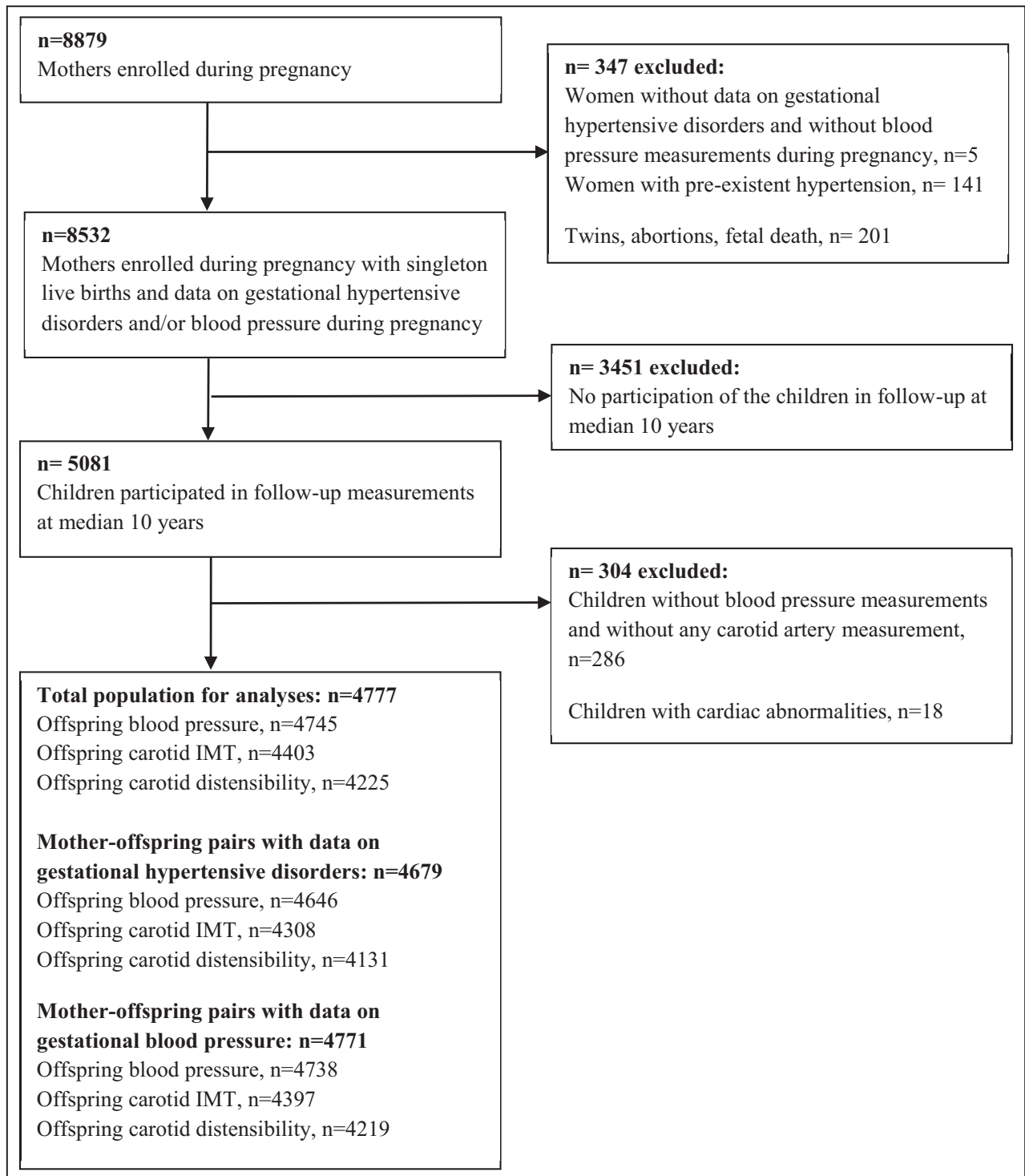


Figure 1. Flowchart of the study population.

Covariates

At enrollment, we collected information on parental age, education level, ethnicity, and maternal folic acid supplementation.²⁰ Maternal prepregnancy weight, parity, smoking, and alcohol consumption during

pregnancy were obtained by prenatal questionnaires. Prepregnancy body mass index (BMI) was calculated using height measured at the intake appointment. Information on gestational age at birth, birth weight, and child sex were obtained from medical records.^{21,22}

Small for gestational age was defined as gestational age–adjusted and sex-adjusted SDSs for birth weights at <10th percentile within our population, and extremely small for gestational age was defined as at <3rd percentile within our population.²² Prematurity was defined as the onset of labor before 37 weeks (either spontaneous or induced). Breastfeeding status was collected by postnatal questionnaires. Child height and weight were measured during the research visit and used to calculate BMI. Age-adjusted and sex-adjusted BMI SD were calculated,²³ and childhood overweight and obesity were classified using the International Obesity Taskforce criteria.²⁴

Statistical Analysis

We examined population characteristics by maternal gestational hypertensive disorder status. We performed a nonresponse analysis to compare characteristics of children with any cardiovascular follow-up data available with those without follow-up data. We constructed SDS for all continuous exposures and outcomes. These SDS were calculated based on the variability in the current study population and represent the equivalent of z scores. We did this to assess the continuous associations of maternal blood pressure per 1 SDS increase with offspring vascular outcomes in SDS and to enable comparisons of effect estimates for all analyses. First, we examined the associations of gestational hypertension and preeclampsia with offspring blood pressure, carotid IMT, and carotid distensibility using linear regression models. Potential confounders and mediators were identified based on previous literature, and relationships were visualized using a directed acyclic graph (Figure S1). To explore the effect of confounders and mediators, we constructed the following 4 different adjustment models: (1) a basic model adjusted for child's age and sex; (2) a confounder model, which is the basic model additionally adjusted for maternal age, parity, prepregnancy BMI, educational level, ethnicity, folic acid supplementation, smoking, and alcohol consumption during pregnancy; (3) a birth model, which is the confounder model additionally adjusted for child's gestational age and weight at birth to explore whether observed associations are explained by these adverse birth outcomes; and (4) a child model, which is the birth model additionally adjusted for breastfeeding status and child BMI at the time of measurements to explore whether observed associations are explained by these child factors. We consider the confounder model the main model, which included covariates selected on their association with exposure and outcome or a change in effect of >10%. Second, we used an unexplained residual model to explore the independent associations of maternal blood pressure in early, mid, and late pregnancy with offspring outcomes.^{25,26} These models take the correlation between maternal blood pressure measurements at

different time points throughout pregnancy into account. Using standardized residuals from linear regression models of maternal blood pressure regressed on all previous blood pressure measurements, maternal SBP and DBP variables were constructed that are statistically independent of each other. This approach allows inclusion of all maternal blood pressure measures simultaneously in 1 regression model. Thus, associations of maternal SBP and DBP in each period with childhood outcomes can be assessed adjusted for, and compared with, maternal SBP and DBP in other periods of pregnancy. We also examined the associations of maternal SBP and DBP in early, mid, and late pregnancy with offspring outcomes separately using regular linear regression models and explored the role of confounders and potential mediators. Third, as a secondary analysis, we examined the associations of paternal early-pregnancy SBP and DBP with offspring outcomes and compared the strength of these paternal–offspring associations with the strength of the maternal–offspring associations. Stronger associations for maternal blood pressure with offspring outcomes would suggest direct intrauterine mechanisms, whereas similar or stronger associations for paternal blood pressure with offspring outcomes would suggest that these associations are more likely to be driven by genetic predisposition or shared lifestyle factors.²⁷ Furthermore, we tested for interactions of gestational hypertensive disorder status and maternal blood pressure with offspring sex, gestational age–adjusted birth weight, and gestational age at birth for all childhood outcomes, but none were significant ($P>0.05$), and no stratified analyses were performed. We performed the following 2 sensitivity analyses: (1) we repeated the maternal blood pressure analyses restricting to a population of normotensive pregnancies to assess whether the found associations are also present for a higher maternal blood pressure across the normal range, and (2) we repeated all analyses excluding children born small for gestational age at <3rd percentile to explore whether associations were driven by severe placental insufficiency as part of the underlying mechanism. We performed multiple imputations for missing data on covariates using the fully conditional specifications method.²⁸ We created 5 independent data sets that were analyzed together and presented the pooled effect estimates. Missing data on covariates were <10% of missing values for covariates, except for folic acid supplementation (23%), breastfeeding status (19%), and prepregnancy BMI (17%). Analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY).

RESULTS

Population Characteristics

Table 1 shows the population characteristics for the total population and by gestational hypertensive

Table 1. Characteristics of the Total Study Population (n=4777)*

Characteristics	Total population n=4777	Normotensive pregnancy n=4410	Gestational hypertension n=184	Preeclampsia n=85	P value*
	Maternal				
Maternal age, y, mean (SD)	30.7 (4.9)	30.7 (4.9)	30.8 (4.8)	29.8 (5.0)	0.20
Prepregnancy BMI, kg/m ² , median (95% range)	22.5 (18.1 to 34.1)	22.4 (18.0 to 33.1)	25.2 (19.4 to 42.5)	23.6 (18.7 to 39.8)	<0.001
Parity, nulliparous, n (%)	2769 (58.3)	2516 (57.3)	136 (73.9)	70 (82.4)	<0.001
Education level, higher, n (%)	2274 (50.2)	2117 (50.6)	83 (46.1)	32 (39.5)	0.07
Ethnicity, European, n (%)	3028 (64.6)	2767 (64.0)	145 (78.8)	53 (63.9)	<0.001
Folic acid supplement use, yes, n (%)	2861 (77.9)	2630 (77.6)	122 (65.3)	54 (76.1)	0.09
Smoking during pregnancy, yes, n (%)	651 (15.3)	601 (15.3)	30 (17.9)	6 (7.7)	0.11
Alcohol consumption during pregnancy, yes, n (%)	1828 (43.3)	1693 (43.5)	75 (45.2)	33 (41.8)	0.87
Systolic blood pressure, mm Hg, mean (SD)					
Early pregnancy	115.5 (11.8)	115.5 (11.5)	124.7 (12.9)	119.7 (12.3)	<0.001
Mid pregnancy	116.7 (11.7)	116.2 (11.4)	127.57 (12.6)	120.4 (12.7)	<0.001
Late pregnancy	118.4 (11.5)	117.8 (11.2)	130.0 (12.4)	125.9 (12.1)	<0.001
Diastolic blood pressure, mm Hg, mean (SD)					
Early pregnancy	68.0 (9.1)	67.6 (8.9)	75.4 (10.5)	72.4 (8.8)	<0.001
Mid pregnancy	67.0 (9.1)	66.5 (8.8)	76.4 (9.7)	73.3 (9.1)	<0.001
Late pregnancy	69.1 (9.1)	68.4 (8.7)	79.4 (9.8)	77.0 (10.0)	<0.001
Paternal					
Age, y, mean (SD)	33.4 (5.5)	33.0 (5.5)	33.4 (5.4)	33.6 (5.8)	0.34
BMI, kg/m ² , median (95% range)	24.9 (19.6 to 32.8)	24.9 (19.6 to 32.6)	26.0 (19.2 to 34.0)	24.7 (19.1 to 35.7)	0.00
Education level, higher, n (%)	1820 (54.7)	1692 (55.3)	71 (46.7)	26 (44.8)	0.04
Ethnicity, European, n (%)	2921 (65.0)	2676 (64.4)	136 (77.3)	51 (67.1)	0.00
Systolic blood pressure, mm Hg, mean (SD)	130.4 (13.5)	129.0 (12.4)	130.3 (13.5)	132.4 (13.3)	0.09
Diastolic blood pressure, mm Hg, mean (SD)	73.4 (10.5)	73.0 (9.1)	73.3 (10.5)	75.3 (11.0)	0.03
Birth and infant					
Female sex, n (%)	2420 (50.7)	2215 (50.2)	98 (53.3)	51 (60.0)	0.15
Gestational age at birth, wk, median (95% range)	40.1 (35.9 to 42.3)	40.1 (36.0 to 42.4)	40.1 (35.3 to 42.3)	38.4 (29.4 to 41.7)	<0.001
Prematurity, n (%)	214 (4.5)	172 (3.9)	8 (4.3)	23 (27.1)	<0.001
Weight at birth, g, median (95% range)	3455 (2556 to 4470)	3475 (2321 to 4475)	3315 (2229 to 4553)	3025 (1015 to 4308)	<0.001
Birth weight z score, mean (SD) [†]	-0.07 (0.98)	-0.05 (0.99)	-0.26 (1.12)	-0.51 (1.08)	<0.001
Small for gestational age <10th percentile, n (%)	10.0 (477)	425 (9.6)	26 (14.1)	18 (21.2)	<0.001
Extremely small for gestational age <3rd percentile, n (%)	3.0 (143)	119 (2.7)	14 (7.6)	9 (10.6)	<0.001

(Continued)

Table 1. Continued

Characteristics	Total population	Normotensive pregnancy	Gestational hypertension	Preeclampsia	P value*
	n=4777	n=4410	n=184	n=85	
Breastfeeding, yes, n (%)	3588 (93.0)	3351 (93.2)	132 (88.0)	63 (92.6)	<0.001
Child					
Age, y, median (95% range)	9.7 (9.4 to 10.7)	9.7 (9.4 to 10.7)	9.7 (9.3 to 11.2)	9.7 (9.4 to 10.8)	0.51
BMI, kg/m ² , median (95% range)	17.0 (14.0 to 24.9)	17.0 (14.0 to 24.7)	17.5 (14.3 to 25.6)	17.5 (13.7 to 29.8)	<0.001
BMI z score, median (95% range) [†]	0.48 (-1.49 to 3.05)	0.47 (-1.49 to 2.99)	0.67 (-1.28 to 3.21)	0.76 (-1.74 to 4.07)	0.01
Overweight (IOTF classification), n (%)	700 (14.7)	636 (14.5)	32 (17.4)	18 (21.2)	0.02
Obese (IOTF classification), n (%)	180 (3.8)	153 (3.5)	11 (6.0)	8 (9.4)	0.02
Systolic blood pressure, mm Hg, mean (SD)	103.1 (7.9)	103.0 (7.9)	105.3 (7.8)	105.5 (9.3)	<0.001
Diastolic blood pressure, mm Hg, mean (SD)	58.6 (6.4)	58.5 (6.4)	60.3 (7.1)	59.65 (6.9)	<0.001
Carotid IMT, mm, mean (SD)	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)	0.46 (0.06)	0.96
Carotid distensibility, kPa ⁻¹ × 10 ⁻³ , median (95% range)	55.9 (39.5 to 79.8)	56.0 (37.1 to 85.6)	54.7 (36.3 to 90.7)	54.4 (34.7 to 91.9)	0.63

BMI indicates body mass index; IMT, intima media thickness; and IOTF, International Obesity Taskforce.

*P values were obtained by ANOVA for continuous variables and by χ^2 for categorical variables.

[†]Birth weight gestational age-adjusted and sex-adjusted standard deviation scores.

[‡]BMI age-adjusted and sex-adjusted standard deviation scores.

disorder status. For the total population, the SBP means (SDs) were 115.5 (11.8), 116.7 (11.7), and 118.4 (11.5) mm Hg in early, mid, and late pregnancy, respectively. The DBP means (SDs) were 68.0 (9.1), 67.0 (9.1), and 69.1 (9.1) mm Hg in early, mid, and late pregnancy, respectively. In total, there were 184 women diagnosed with gestational hypertension and 85 women with preeclampsia. Women with gestational hypertension or preeclampsia had higher blood pressure levels in each pregnancy period when compared with women with a normotensive pregnancy. Table S1 shows that compared with the population for analysis, mothers of offspring without follow-ups at the age of 10 years were younger, lower educated, and more often from non-European descent. They had a slightly lower SBP and DBP, a slightly higher prevalence of preeclampsia, and lower prevalence of gestational hypertension.

Gestational Hypertensive Disorders With Offspring Blood Pressure, Carotid IMT, and Carotid Distensibility

Table 2 shows that offspring of mothers who developed gestational hypertension had a higher SBP and DBP compared with offspring from mothers with a normotensive pregnancy in the confounder model (differences of 0.17 SDS [95% CI, 0.02–0.31] and 0.23 SDS [95% CI, 0.08–0.38] in offspring SBP and DBP, respectively), but no differences in offspring carotid IMT and distensibility were present. Additional adjustments for gestational age and weight at birth, breastfeeding, or child adiposity did not explain these findings. Offspring of mothers who developed preeclampsia only had a higher SBP compared with offspring from mothers with a normotensive pregnancy (difference of 0.23 [95% CI, 0.02–0.44] SDS in offspring SBP), but no differences in offspring DBP, carotid IMT, and distensibility were present. The association of preeclampsia with offspring SBP attenuated toward the null after additional adjustment for birth and child factors.

Maternal Blood Pressure in Different Periods of Pregnancy With Offspring Blood Pressure, Carotid IMT, and Carotid Distensibility

Figure 2 shows the independent associations of maternal blood pressure in early, mid, and late pregnancy with offspring outcomes from unexplained residual models (effect estimates with 95% CIs shown in Table S2). Higher maternal SBP and DBP in early and mid pregnancy, but not late pregnancy, were independently associated with higher offspring SBP and DBP and lower carotid distensibility (all $P < 0.05$). No associations were present for maternal blood pressure in different periods of pregnancy with offspring carotid IMT.

Table 2. Associations of Gestational Hypertension and Preeclampsia With Offspring Blood Pressure, Carotid IMT, and Carotid Distensibility at a Median Age of 10 Years (n=4679)*

Offspring outcomes	Normotensive pregnancy	Gestational hypertension				Preeclampsia			
		Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS† (n=4646)	Reference	0.28 (0.14 to 0.43)†	0.17 (0.02 to 0.31)§	0.17 (0.02 to 0.31)§	0.16 (0.02 to 0.30)§	0.32 (0.11 to 0.53)§	0.23 (0.02 to 0.44)§	0.19 (-0.03 to 0.40)	0.12 (-0.08 to 0.32)
DBP, SDS† (n=4646)	Reference	0.27 (0.13 to 0.42)†	0.23 (0.08 to 0.38)§	0.22 (0.07 to 0.37)§	0.22 (0.07 to 0.38)§	0.17 (-0.04 to 0.38)	0.12 (-0.09 to 0.34)	0.08 (-0.14 to 0.29)	0.06 (-0.16 to 0.27)
IMT, SDS‡ (n=4131)	Reference	-0.02 (-0.17 to 0.13)	0.01 (-0.15 to 0.16)	0.03 (-0.12 to 0.19)	0.04 (-0.12 to 0.19)	0.03 (-0.19 to 0.24)	0.03 (-0.19 to 0.24)	0.10 (-0.12 to 0.32)	0.09 (-0.13 to 0.31)
Distensibility, SDS† (n=4308)	Reference	-0.07 (-0.22 to 0.09)	-0.02 (-0.18 to 0.14)	-0.04 (-0.20 to 0.12)	-0.05 (-0.20 to 0.11)	-0.09 (-0.31 to 0.14)	-0.06 (-0.29 to 0.16)	-0.11 (-0.33 to 0.12)	-0.08 (-0.30 to 0.15)

DBP indicates diastolic blood pressure; IMT, intima media thickness; SBP, systolic blood pressure; and SDS, standard deviation score.

*Values are regression coefficients (95% CIs) that were obtained from regular multivariable linear regression models and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS), and carotid distensibility (SDS) for gestational hypertension and preeclampsia. Groups are compared with women with a normotensive pregnancy as reference. Estimates are from multiple imputed data. Basic models are adjusted for child's age and sex. Confounder model is a basic model additionally adjusted for maternal age, parity, prepregnancy body mass index, educational level, maternal ethnicity, folic acid supplementation, smoking, and alcohol consumption during pregnancy. Birth model is a confounder model additionally adjusted for child's gestational age and weight at birth. Child model is a birth model additionally adjusted for offspring breastfeeding status and body mass index at time of the measurements.

†Study population for offspring blood pressure with 184 cases of gestational hypertension and 85 cases of preeclampsia.

‡P<0.001.

§P<0.05.

¶Study population for offspring IMT with 165 cases of gestational hypertension and 77 cases of preeclampsia.

‡Study population for offspring distensibility with 174 cases of gestational hypertension and 83 cases of preeclampsia.

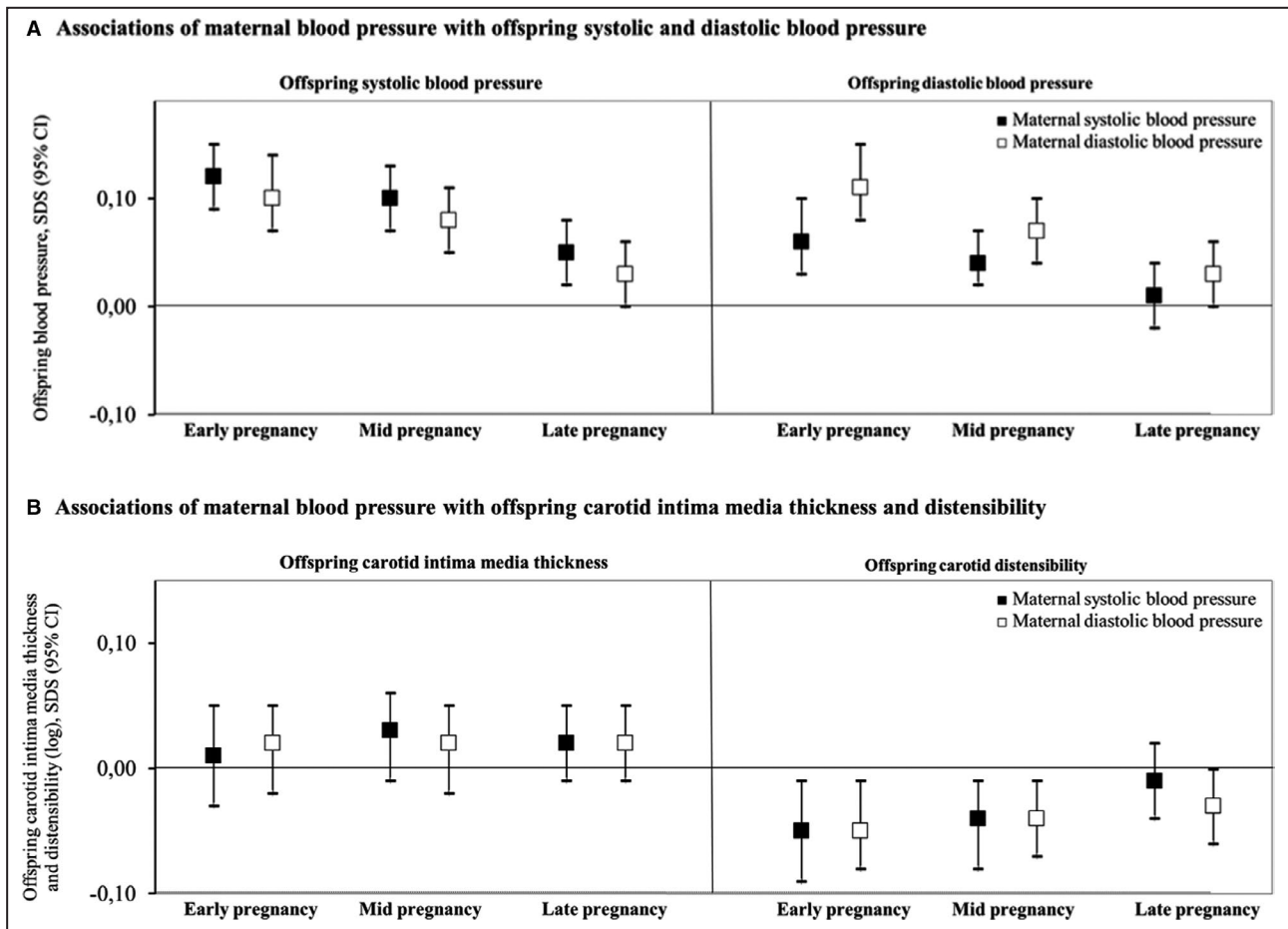


Figure 2. Associations of maternal blood pressure during pregnancy with (A) child blood pressure and (B) carotid IMT and distensibility from unexplained residual models (n=4771).

Values are regression coefficients (95% CI) and reflect the difference in offspring blood pressure (SDS), carotid IMT (SDS), and carotid distensibility (SDS) per 1 SDS change in maternal early-pregnancy blood pressure and per SDS change in standardized residual change in maternal blood pressure in mid and late pregnancy from unexplained residual models. Estimates are from multiple imputed data. Maternal blood pressure was additionally imputed for women with at least 1 blood pressure measurement in pregnancy. Models are adjusted for child's age and sex, gestational age at intake, maternal age, parity, prepregnancy body mass index, educational level, maternal ethnicity, folic acid supplementation, smoking, and alcohol consumption during pregnancy. SDS indicates standard deviation score.

Role of Maternal Factors, Birth Outcomes, Breastfeeding, and Childhood Adiposity

Table 3 shows the associations of maternal early-pregnancy, mid-pregnancy, and late-pregnancy SBP and DBP with offspring outcomes per 1 SDS change using regular linear regression models and the role of confounders and potential mediators. In the confounder model, higher maternal SBP and DBP in early, mid, and late pregnancy were associated with increased offspring SBP and DBP and decreased offspring carotid distensibility (all $P < 0.05$), but not with offspring carotid IMT. For example, 1 SDS increase in maternal early-pregnancy SBP, which corresponds to 11.8 mm Hg, was related to 0.11 SDS increase in offspring SBP, 0.06 increase in DBP, and 0.04 decrease in carotid distensibility. Additional adjustments for gestational age and

weight at birth, breastfeeding, and child adiposity did not explain these associations. To investigate if the associations of maternal blood pressure with offspring blood pressure were explained by decreased distensibility, we additionally adjusted these analyses for offspring distensibility, which led to a small attenuation of the effect estimates for SBP only (Table S3). To investigate if the associations of maternal blood pressure with offspring distensibility were explained by offspring blood pressure, we additionally adjusted these analyses for offspring mean arterial pressure, which led to a small attenuation of the effect estimates (Table S4).

Higher paternal early-pregnancy SBP and DBP were associated with increased offspring SBP and DBP, increased carotid IMT, and decreased distensibility (all $P < 0.05$; Table S5). The paternal associations with

Table 3. Associations of Maternal Blood Pressure With Offspring Blood Pressure, Carotid IMT, and Carotid Distensibility at a Median Age of 10 Years (n=4771)*

Offspring outcomes	Early-pregnancy maternal SBP					Mid-pregnancy maternal SBP					Late-pregnancy maternal SBP				
	Basic	Confounder	Birth	Child		Basic	Confounder	Birth	Child		Basic	Confounder	Birth	Child	
SBP, SDS [†]	0.13 (0.10 to 0.17) [‡]	0.11 (0.06 to 0.14) [‡]	0.11 (0.07 to 0.14) [‡]	0.10 (0.06 to 0.13) [‡]		0.16 (0.13 to 0.19) [‡]	0.14 (0.11 to 0.17) [‡]	0.14 (0.11 to 0.17) [‡]	0.12 (0.09 to 0.15) [‡]		0.14 (0.11 to 0.17) [‡]	0.11 (0.08 to 0.14) [‡]	0.11 (0.08 to 0.14) [‡]	0.09 (0.06 to 0.12) [‡]	
DBP, SDS [†]	0.07 (0.04 to 0.10) [‡]	0.06 (0.02 to 0.09) [‡]	0.06 (0.02 to 0.09) [‡]	0.05 (0.02 to 0.09) [‡]		0.08 (0.05 to 0.11) [‡]	0.07 (0.04 to 0.10) [‡]	0.07 (0.04 to 0.10) [‡]	0.06 (0.03 to 0.09) [‡]		0.05 (0.02 to 0.08) [‡]	0.04 (0.01 to 0.07) [‡]	0.04 (0.01 to 0.07) [‡]	0.03 (0.00 to 0.06) [‡]	
IMT, SDS [‡]	-0.00 (-0.04 to 0.03)	0.01 (-0.02 to 0.05)	0.01 (-0.02 to 0.05)	0.01 (-0.02 to 0.05)		0.01 (-0.03 to 0.04)	0.02 (-0.01 to 0.06)	0.02 (-0.01 to 0.05)	0.02 (-0.01 to 0.05)		0.01 (-0.02 to 0.04)	0.03 (-0.00 to 0.06)	0.03 (-0.00 to 0.06)	0.03 (-0.01 to 0.06)	
Distensibility, SDS [‡]	-0.05 (-0.10 to -0.02)	-0.04 (-0.08 to -0.01) [‡]	-0.04 (-0.09 to 0.00)	-0.04 (-0.08 to -0.00) [‡]		-0.07 (-0.10 to -0.04) [‡]	-0.06 (-0.09 to -0.03) [‡]	-0.07 (-0.11 to -0.03) [‡]	-0.05 (-0.09 to -0.02) [‡]		-0.05 (-0.08 to -0.02) [‡]	-0.04 (-0.07 to -0.00) [‡]	-0.04 (-0.08 to 0.00)	-0.03 (-0.06 to 0.01)	
Offspring outcomes	Early-pregnancy maternal DBP					Mid-pregnancy maternal DBP					Late-pregnancy maternal DBP				
	Basic	Confounder	Birth	Child		Basic	Confounder	Birth	Child		Basic	Confounder	Birth	Child	
SBP, SDS [†]	0.13 (0.10 to 0.16) [‡]	0.09 (0.06 to 0.13) [‡]	0.09 (0.06 to 0.13) [‡]	0.09 (0.06 to 0.12) [‡]		0.16 (0.13 to 0.19) [‡]	0.12 (0.09 to 0.15) [‡]	0.12 (0.09 to 0.15) [‡]	0.11 (0.08 to 0.13) [‡]		0.13 (0.10 to 0.15) [‡]	0.09 (0.06 to 0.12) [‡]	0.09 (0.06 to 0.12) [‡]	0.07 (0.04 to 0.10)	
DBP, SDS [†]	0.12 (0.09 to 0.15) [‡]	0.10 (0.07 to 0.14) [‡]	0.10 (0.07 to 0.14) [‡]	0.10 (0.07 to 0.14) [‡]		0.13 (0.10 to 0.16) [‡]	0.11 (0.08 to 0.14) [‡]	0.11 (0.07 to 0.14) [‡]	0.10 (0.07 to 0.13) [‡]		0.11 (0.08 to 0.14) [‡]	0.09 (0.06 to 0.12) [‡]	0.09 (0.06 to 0.12) [‡]	0.08 (0.05 to 0.11) [‡]	
IMT, SDS [‡]	-0.00 (-0.03 to 0.04)	0.02 (-0.02 to 0.05)	0.02 (-0.01 to 0.06)	0.02 (-0.01 to 0.06)		0.01 (-0.02 to 0.04)	0.02 (-0.01 to 0.05)	0.02 (-0.01 to 0.05)	0.02 (-0.01 to 0.05)		0.02 (-0.01 to 0.05)	0.03 (-0.00 to 0.06)	0.04 (0.00 to 0.07) [‡]	0.03 (0.00 to 0.07) [‡]	
Distensibility, SDS [‡]	-0.04 (-0.08 to -0.01) [‡]	-0.04 (-0.08 to -0.00) [‡]	-0.04 (-0.08 to -0.00) [‡]	-0.04 (-0.08 to -0.00) [‡]		-0.07 (-0.10 to -0.04) [‡]	-0.06 (-0.09 to -0.03) [‡]	-0.06 (-0.09 to -0.02) [‡]	-0.05 (-0.08 to -0.01) [‡]		-0.06 (-0.09 to -0.03) [‡]	-0.06 (-0.09 to -0.03) [‡]	-0.06 (-0.09 to -0.03) [‡]	-0.05 (-0.08 to -0.02) [‡]	

DBP indicates diastolic blood pressure; IMT, intima media thickness; SBP, systolic blood pressure; and SDS, standard deviation score.

*Values are regression coefficients (95% CIs) that were obtained from regular multivariable linear regression models and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS), and carotid distensibility (SDS) per SDS change in maternal blood pressure. Estimates are from multiple imputed data. Basic model is adjusted for child's age and sex and gestational age at the time of blood pressure measurements. Confounder model is a basic model additionally adjusted for maternal age, parity, prepregnancy body mass index, educational level, maternal ethnicity, folic acid supplementation, smoking, and alcohol consumption during pregnancy. Birth model is a confounder model additionally adjusted for child's gestational age and weight at birth. Child model is a birth model additionally adjusted for offspring breastfeeding status and body mass index at time of the measurements.

[†]Study population for offspring blood pressure: n=3727 for early pregnancy, n=4487 for mid pregnancy, n=4577 for late pregnancy.

[‡]p<0.001.

[§]p<0.05.

[¶]Study population for offspring IMT: n=3448 for early pregnancy, n=4166 for mid pregnancy, n=4249 for late pregnancy.

[‡]Study population for offspring distensibility: n=3298 for early pregnancy, n=3990 for mid pregnancy, n=4076 for late pregnancy.

offspring blood pressure and carotid distensibility were comparable in strength with the maternal–offspring associations. When we included both maternal and paternal early-pregnancy blood pressures in the same model, both the maternal–offspring and paternal–offspring associations remained significant, and the effect estimate was comparable in magnitude (all $P < 0.05$; Table S6).

Sensitivity Analyses

When we restricted to a population of normotensive pregnancies, we found similar associations for gestational blood pressure in early, mid, and late pregnancy with offspring outcomes (Table S7). When we excluded children born small for gestational age at <3rd percentile, we found similar associations for gestational hypertensive disorder status and gestational blood pressure in early, mid, and late pregnancy with offspring outcomes (Tables S8 and S9).

DISCUSSION

We observed that offspring exposed to maternal gestational hypertension and a higher maternal gestational blood pressure, already within the normal and prehypertension range, had higher SBP and DBP and lower carotid distensibility at the age of 10 years. No differences in carotid IMT were present. Maternal SBP and DBP in early and mid pregnancy, but not late pregnancy, were independently associated with these offspring outcomes. No associations were present for preeclampsia. These findings were not explained by maternal, birth, or child factors. However, as the maternal blood pressure and paternal blood pressure associations with these offspring outcomes were comparable in strength, these associations are more likely driven by genetic predisposition and shared lifestyle rather than by a direct intrauterine effect.

Methodological Considerations

Strengths of our study are prospective data collection from early pregnancy to school age; a large sample size; repeated maternal blood pressure measurements during early, mid, and late pregnancy; and the availability of paternal blood pressure at study enrollment. From the mothers with singleton-life births and available information on the exposures during pregnancy, 56% of the children participated in the current study. Compared with the population for analysis, mothers of offspring without childhood follow-up had slightly lower SBP and DBP, a higher prevalence of preeclampsia, and a lower prevalence of gestational hypertension. These differences were only small and not of clinical relevance. Still, possible self-selection of children who were healthier could have occurred, but we are not able to assess this with the information that we have

available within our study. A selective nonresponse could have led to biased effect estimates if associations would be different between the included children and nonincluded children, but this does not seem likely. We had relatively small numbers of gestational hypertension and preeclampsia, which might have led to reduced statistical power for the gestational hypertensive disorder analyses. Our prevalence of gestational hypertensive disorders was slightly lower when compared with the general Dutch population, this may be attributed to the exclusion of preexisting hypertension from the current study. Not all women had 3 blood pressure measurements during pregnancy available as a result of later enrollment or because they missed a physical examination. To avoid a reduction of statistical power for the unexplained residual models, we imputed the maternal blood pressure measurements for these analyses only. When we compared the results of the imputed versus the complete-case analyses, the effect estimates were similar. Because of the design of our cohort and limited time available during research visits, the child's blood pressure was measured during the ultrasound of the common carotid artery in supine position. Absolute blood pressure values might have been lower if they had been measured in a seated position, which is the standard position in clinical practice for children's blood pressure measurement at the age of 10 years.²⁹ In our study, we were interested in relative blood pressure differences by maternal gestational blood pressure levels among a group of children, which makes it unlikely that the method of measurement biased our results. Of the children, 7.6% and 18.6% did not have 3 measurements on both sides of the common carotid artery for calculation of the carotid IMT and distensibility, respectively. This was attributed to low-quality recordings or missing coinciding cardiac cycles. We included all children with at least 1 reliable carotid IMT or distensibility measurement in our main analyses. When we repeated the analyses among children with all 3 measurements on both sides available, we observed similar results (results not shown). We did not adjust for multiple testing because the childhood outcomes are strongly correlated. Finally, we had detailed information on a large number of covariates. Although we accurately tried to control for confounding, the observational nature of the study still leaves a possibility for residual confounding because of unmeasured lifestyle factors or family history.

Interpretation of Main Findings

Gestational hypertensive disorders are an important risk factor for adverse birth outcomes and are associated with higher blood pressure in mothers and offspring in later life. Results from animal studies suggest that exposure to an adverse intrauterine environment

induced by impaired gestational hemodynamic adaptations might lead to atherosclerotic vascular alterations and higher blood pressure in the offspring, but only a few studies investigated this among human populations. Carotid IMT and distensibility are sensitive markers to investigate atherosclerotic changes in pediatric and adult populations.^{30,31} Carotid IMT primarily reflects the formation of fatty streaks by the accumulation of lipids in the intima media of the common carotid artery, whereas carotid distensibility is inversely related to arterial stiffness.³⁰ Carotid IMT and carotid distensibility are both strongly associated with systemic atherosclerosis.³² These subclinical atherosclerotic markers have been associated with higher blood pressure in adulthood and an increased risk of all-cause cardiovascular mortality.^{33,34} We hypothesized that offspring exposed to gestational hypertensive disorders and higher gestational blood pressure, even below the diagnostic threshold for gestational hypertensive disorders, are at risk of these adverse atherosclerotic changes, predisposing them to a higher blood pressure.

A recent systematic review of 10 studies concluded that gestational hypertension is associated with higher offspring blood pressure during childhood and adolescence, but these associations were inconsistent for offspring of pregnancies affected by preeclampsia.³ Only a few studies investigated the direct effects on offspring vascular development in response to maternal gestational hypertensive disorders. A study among 138 children aged 14 years and permanently living at high altitude in Bolivia found that pulmonary artery pressure was higher and brachial artery flow-mediated dilation was smaller in offspring from pregnancies affected by preeclampsia compared with normotensive pregnancies.¹² Likewise, a study from the United Kingdom among 71 subjects born preterm found that those who were exposed to preeclampsia or gestational hypertension had increased carotid IMT and flow-mediated dilatation at the age of 20 years.¹⁰ Two small studies found that neonates exposed to preeclampsia had an increased aortic IMT when compared with normotensive pregnancies.^{9,11} In these studies, no extensive adjustment for confounders was performed. In contrast, in a study among ≈4000 mother–offspring pairs from the United Kingdom, no associations of gestational hypertensive disorders with brachial artery flow-mediated dilatation, brachial pulse wave velocity, or brachial distensibility in children aged 9 to 12 years were observed.² Partly in line with these previous studies, we observed that gestational hypertension, but not preeclampsia, was associated with higher offspring blood systolic and diastolic pressure at the age of 10 years, independent of maternal, birth, or childhood factors. We did not find any associations for gestational hypertension or preeclampsia with

offspring carotid IMT and distensibility. Differences between our study and the previous studies may relate to the timing of vascular assessment. Neonatal aortic intima media thickening might only reflect a temporary alteration in a response to insufficient placental flow in preeclamptic pregnancies that does not persist into childhood.^{11,35} Furthermore, fatty deposits in the carotid intima media only first emerge during early adolescence and may not yet be detectable at the age of 10 years.³⁶ Thus, we found that offspring exposed to gestational hypertension, but not preeclampsia, had increased SBP and DBP at the age of 10 years when compared with offspring from normotensive pregnancies, but they did not display early signs of atherosclerotic vascular changes.

Gestational hypertension and preeclampsia represent the extremes of the gestational hypertensive disorder spectrum, but already a higher maternal blood pressure below the clinical threshold for gestational hypertensive disorders may be associated with a higher offspring blood pressure.^{5,6} In line with our findings for gestational hypertension, we observed that higher maternal gestational SBP and DBP across the full spectrum were associated with increased offspring SBP and DBP and decreased carotid distensibility. These associations were also present when we restricted to a population of normotensive pregnancies. We observed the strongest and independent effects for maternal early-pregnancy and mid-pregnancy SBP and DBP. This is in line with a previous study within our observational cohort that focused on the associations of maternal gestational blood pressure with childhood blood pressure among children aged 6 years.⁵ Similarly, a study among 6619 mother–offspring pairs from the United Kingdom and a Danish study among 2217 mother–offspring pairs also found a positive association of early-pregnancy maternal SBP and DBP with offspring SBP and DBP in infancy, childhood, and adolescence.^{6,37} No previous study explored the direct effects of maternal gestational blood pressure on offspring vascular properties of large arteries. We observed that higher maternal gestational blood pressure across the full spectrum was associated with decreased carotid distensibility in the offspring, with the strongest effect in early and mid pregnancy. When we adjusted the offspring blood pressure analyses for carotid distensibility, effect estimates for offspring SBP partly attenuated. This suggests that early functional offspring vascular changes might represent steps in the pathophysiological pathway, predisposing offspring to a higher SBP also later in life. However, the effect estimates for carotid distensibility also partly attenuated when these analyses were additionally adjusted for mean arterial pressure. As offspring blood pressure and carotid distensibility were measured at the same time, it is difficult to disentangle how arterial

stiffness may influence offspring blood pressure and vice versa. Further studies should focus on the relation between blood pressure levels and arterial stiffness in children and whether arterial stiffness is a cause or consequence of higher blood pressure levels. It is known that in an early stage of cardiovascular disease the formation of fatty streaks in the carotid intima media are preceded by functional vascular changes related to arterial stiffness, which may explain why we did not find an association with carotid IMT.³⁰

Our findings suggest that maternal gestational hypertension and higher gestational blood pressure, even below the diagnostic threshold for gestational hypertensive disorders, might influence offspring blood pressure and arterial stiffness at the age of 10 years. These observed associations may be explained by several mechanisms. The associations for gestational hypertension and maternal gestational blood pressure with offspring outcomes were not explained by maternal sociodemographic and lifestyle factors or mediated by gestational age and weight at birth, breastfeeding, or child adiposity. In contrast, the only observed effect of preeclampsia with offspring SBP attenuated toward the null after additional adjustments for gestational age at birth and birth weight. Preeclampsia is a well-known risk factor for preterm birth and small for gestational age at birth, both birth outcomes that are associated with increased blood pressure in later life. Our findings suggest that the associations of preeclampsia with higher offspring SBP are explained by these adverse birth outcomes. This is in line with the findings from other large observational studies.^{3,38} Animal studies suggest that fetal exposure to an adverse intrauterine environment from early gestation may lead to atherosclerotic vascular remodeling in the offspring.⁸ However, atherosclerotic changes in the offspring can also be explained by shared genetic predisposition or lifestyle factors in mother–offspring pairs, especially as mothers who suffered gestational hypertension or preeclampsia also have an increased risk of cardiovascular disease in later life. When we compared the strength of the maternal–offspring and paternal–offspring associations with offspring blood pressure and distensibility, the associations for maternal and paternal blood pressures were similar. This suggests that the associations of maternal gestational blood pressure with offspring blood pressure and arterial stiffness are more likely to be driven by shared genetic predisposition or lifestyle factors between mother and child rather than by a direct intrauterine effect. We found similar associations when we repeated the analyses excluding children born extremely small for gestational age; these findings further contradict a direct intrauterine effect as the underlying mechanism for the found associations. Despite animal studies identifying early pregnancy as a critical period for fetal vascular developmental adaptations, maternal

blood pressure levels during early and mid pregnancy might also reflect maternal genetic predisposition to a higher blood pressure, whereas this is reflected less by late-pregnancy blood pressure when more gestational hemodynamic adaptations have taken place.³⁹ In a previous study among 3748 children within our cohort, we found that gestational hypertensive disorders and gestational blood pressure influence offspring retinal vessel calibers at the age of 6 years, with stronger maternal–offspring rather than paternal–offspring associations.⁷ Based on findings from this previous study and our current study, higher maternal blood pressure levels in pregnancy might have a direct effect on offspring microvasculature development, but to a lesser extent on offspring vascular properties of large arteries. Further observational and experimental studies need to focus on disentangling the underlying mechanisms for microvascular and macrovascular changes in the offspring in response to maternal gestational blood pressure and critical periods for exposure to a higher maternal blood pressure during pregnancy.

Perspectives

Maternal gestational hypertension and higher maternal gestational blood pressure across the full blood pressure spectrum are associated with higher childhood blood pressure and lower carotid distensibility. This suggests that differences in arterial stiffness may already be present in their offspring from childhood onward. No associations were found for preeclampsia with offspring vascular outcomes. The strongest effects were present for maternal blood pressure in early and mid pregnancy. These findings were not explained by maternal, birth, or child factors. As the strength of the associations of maternal and paternal blood pressures with offspring vascular outcomes were comparable, these associations are most likely driven by shared genetic predisposition and lifestyle factors between mothers and offspring rather than a direct intrauterine effect.

Although the observed associations are relatively small, our findings are important on a population level and from a public health perspective. Higher blood pressure is known to track from childhood into adulthood.⁴⁰ Higher blood pressure and increased arterial stiffness during adulthood are strong independent predictors for hypertension, myocardial infarction, stroke, and all-cause cardiovascular mortality.^{33,34,41,42} Our study suggests that the maternal gestational blood pressure profile might be useful for early identification of offspring at increased risk of an adverse cardiovascular risk profile in later life. These children may benefit from prevention strategies focused on reducing risk factors for cardiovascular diseases from early life onward. Further studies are needed to investigate

the long-term offspring cardiovascular consequences and the potential of using maternal gestational blood pressure in screening tools for the early identification of children at increased risk of cardiovascular diseases.

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Author contributions: Wiertsema and Gaillard were responsible for the study design, performed the statistical analyses, and wrote the manuscript and had primary responsibility for the final content. Jaddoe and Mulders contributed to the design of the study and interpretation of the results and were responsible for the critical review of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Disclosures

None.

Supplemental Material

Tables S1–S9
Figure S1

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Supplemental Material

Table S1. Non-response analysis: Baseline characteristics for the total study population with offspring with blood pressure and carotid ultrasound follow-up vs. baseline characteristics of population without offspring cardiovascular follow-up at 10 years.

	Follow-up at 10 years <i>n=4777</i>	No follow-up at 10 years* <i>n=3737</i>
<u>Maternal characteristics</u>		
Maternal age, mean (sd), years	30.7 (4.9)	28.2 (5.5)
Prepregnancy BMI, median (95% range), kg/m ²	22.5 (18.1, 34.1)	22.7 (17.7, 35.5)
Parity, n nulliparous (%)	2769 (58.3)	1903 (52.2)
Education level, n higher (%)	2274 (50.2)	970 (30.4)
Ethnicity, n European (%)	3028 (64.6)	1532 (46.0)
Folic acid supplement use, n yes (%)	2861 (77.9)	1571 (60.0)
Smoking during pregnancy, n yes (%)	651 (15.3)	729 (19.5)
Alcohol consumption during pregnancy, n yes (%)	1828 (43.3)	868 (23.2)
Preeclampsia, n yes (%)	85 (1.9)	84 (2.5)
Gestational hypertension, n yes (%)	184 (4.0)	121 (3.5)
Systolic blood pressure, mean (sd), mmHg		
Early-pregnancy	115.5 (11.8)	114.8 (12.3)
Mid-pregnancy	116.7 (11.7)	115.9 (12.1)
Late-pregnancy	118.4 (11.5)	117.4 (12.4)
Diastolic blood pressure, mean (sd), mmHg		
Early-pregnancy	68.0 (9.1)	67.8 (9.6)
Mid-pregnancy	67.0 (9.1)	66.9 (9.4)
Late-pregnancy	69.1 (9.1)	68.5 (9.3)
<u>Paternal characteristics</u>		
Age, mean (sd), years	33.4 (5.5)	31.6 (6.0)
BMI, median (95% range), kg/m ²	24.9 (19.6, 32.8)	25.1 (19.2, 33.8)
Education level, n higher (%)	1820 (54.7)	746 (43.2)
Ethnicity, n European (%)	2921 (65.0)	1363 (46.4)
Systolic blood pressure, mean (sd), mmHg	130.4 (13.5)	129.5 (13.5)
Diastolic blood pressure, mean (sd), mmHg	73.4 (10.5)	73.0 (10.9)
<u>Birth and infant characteristics</u>		
Sex, n female (%)	2420 (50.7)	1774 (48.1)
Gestational age at birth, median (95% range), weeks	40.1 (35.9, 42.3)	40.0 (35.3, 42.3)
Prematurity, n (%)	214 (4.5)	223 (6.0)
Weight at birth, median (95% range), grams	3455 (2556, 4470)	3390 (2217, 4500)
Breastfeeding, n yes (%)	3588 (93.0)	1877 (90.8)

BMI, body mass index. Values are mean (sd), median (95% range), or number (%).

*Baseline characteristics of the population that enrolled during pregnancy but did not attend at the follow-up visit at 10 year (n=3451), or no measurements done during the visit at 10 years (n=286). Children with cardiac abnormalities are excluded from this analyses.

Table S2. Associations of maternal blood pressure with offspring blood pressure, carotid intima media thickness and carotid distensibility at median 10 years from conditional change analyses (n=4771)*

Offspring outcomes	Maternal SBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
SBP, SDS n=4738	0.12 (0.09, 0.15)**	0.10 (0.07, 0.13)**	0.05 (0.02, 0.08)*
DBP, SDS n=4738	0.06 (0.03, 0.10)**	0.04 (0.02, 0.07)*	0.01 (-0.02, 0.04)
IMT, SDS n=4397	0.01 (-0.03, 0.05)	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.05)
Distensibility, SDS n=4219	-0.05 (-0.09, -0.01)*	-0.04 (-0.08, -0.01)*	-0.01 (-0.04, 0.02)

Offspring outcomes	Maternal DBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
SBP, SDS n=4738	0.10 (0.07, 0.14)**	0.08 (0.05, 0.11)**	0.03 (-0.00, 0.06)
DBP, SDS n=4738	0.11 (0.08, 0.15)**	0.07 (0.04, 0.10)**	0.03 (0.00, 0.06)
IMT, SDS n=4397	0.02 (-0.02, 0.05)	0.02 (-0.02, 0.05)	0.02 (-0.01, 0.05)
Distensibility, SDS n=4219	-0.05 (-0.08, -0.01)*	-0.04 (-0.07, -0.01)*	-0.03 (-0.06, 0.00)

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. **P* value <0.05. ** *P* value <0.001.

* Values are regression coefficients (95% confidence interval) that reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS) and carotid distensibility (SDS) per SDS change in maternal early-pregnancy blood pressure, and per SDS change in standardized residual change in maternal blood pressure in mid and late-pregnancy from conditional change models. Estimates are from multiple imputed data. Maternal blood pressure was additionally imputed for women with at least one blood pressure measurement in pregnancy. Models are adjusted for child's age and sex, gestational age at intake, maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation, smoking and alcohol consumption during pregnancy.

Table S3. Associations of maternal blood pressure with offspring blood pressure adjusted for offspring distensibility (n=4219)*

Offspring outcomes	Maternal SBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
SBP, SDS	0.09 (0.06, 0.12)**	0.10 (0.08, 0.13)**	0.08 (0.05, 0.11)**
DBP, SDS	0.07 (0.03, 0.10)**	0.06 (0.03, 0.09)**	0.04 (0.00, 0.06)*

Offspring outcomes	Maternal DBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
SBP, SDS	0.07 (0.04, 0.11)**	0.09 (0.06, 0.12)**	0.06 (0.03, 0.09)*
DBP, SDS	0.10 (0.06, 0.14)**	0.11 (0.08, 0.14)**	0.09 (0.05, 0.11)**

SBP, systolic blood pressure. DBP, diastolic blood pressure. **P* value <0.05. ** *P* value <0.001.

*Values are regression coefficients (95% confidence interval) that were obtained from regular multivariable linear regression models with maternal blood pressure as SDS, and reflect the differences in offspring blood pressure (SDS) per SDS change in maternal blood pressure. Estimates are from multiple imputed data (distensibility not imputed). Models are adjusted for child's age and sex, gestational age at the time of maternal blood pressure measurements, maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation, smoking and alcohol consumption during pregnancy, child's gestational age and weight at birth, breastfeeding status, offspring BMI and distensibility. Study population with data on offspring blood pressure and carotid distensibility: n=3288 for early-pregnancy, n=3972 for mid-pregnancy, n=4059 for late-pregnancy.

Table S4. Associations of maternal blood pressure with offspring distensibility adjusted for offspring mean arterial pressure (n=4219).

Offspring outcomes	Maternal SBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
Distensibility, SDS	-0.04 (-0.07, 0.00)	-0.05 (-0.08, -0.01)*	-0.02 (-0.05, 0.01)

Offspring outcomes	Maternal DBP		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
Distensibility, SDS	-0.03 (-0.07, 0.00)	-0.05 (-0.08, -0.01)*	-0.04 (-0.08, -0.01)*

**P* value <0.05.

*Values are regression coefficients (95% confidence interval) that were obtained from regular multivariable linear regression models with maternal blood pressure as SDS, and reflect the differences in offspring distensibility (SDS) per SDS change in maternal blood pressure. Estimates are from multiple imputed data (mean arterial pressure not imputed). Models are adjusted for child's age and sex, gestational age at the time of maternal blood pressure measurements, maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation, smoking and alcohol consumption during pregnancy, child's gestational age and weight at birth, breastfeeding status, offspring BMI and mean arterial pressure. Study population with data on offspring carotid distensibility and mean arterial pressure: n=3288 for early-pregnancy, n=3972 for mid-pregnancy, n=4059 for late-pregnancy.

Table S5. Associations of paternal blood pressure with offspring blood pressure, carotid intima media thickness and carotid distensibility at median 10 years (n=3518)*

Offspring outcomes	Paternal SBP			
	Basic model	Confounder model	Birth model	Child model
SBP, SDS n=3518	0.13 (0.10,0.16)**	0.11 (0.07, 0.14)**	0.11 (0.07, 0.14)**	0.12 (0.09, 0.15)**
DBP, SDS n=3518	0.04 (0.01, 0.07)*	0.04 (0.01, 0.08)*	0.04 (0.01, 0.08)*	0.05 (0.01, 0.08)*
IMT, SDS n=3276	0.04 (0.01, 0.07)*	0.04 (0.01, 0.08)*	0.04 (0.00, 0.08)*	0.04 (0.01, 0.08)*
Distensibility, SDS n=3124	-0.08 (-0.11,-0.05)**	-0.05 (-0.10, -0.02)*	-0.06 (-0.09, -0.02)*	-0.06 (-0.10, -0.03)*
Offspring outcomes	Paternal DBP			
	Basic model	Confounder model	Birth model	Child model
SBP, SDS n=3518	0.09 (0.06, 0.13)**	0.08 (0.05, 0.11)**	0.08 (0.05, 0.11)**	0.10 (0.06, 0.13)**
DBP, SDS n=3518	0.09 (0.06, 0.12)**	0.10 (0.07, 0.14)**	0.10 (0.07, 0.14)**	0.11 (0.07, 0.14)**
IMT, SDS n=3276	0.03 (-0.00, 0.07)	0.03(-0.01, 0.07)	0.03 (-0.00, 0.07)	0.04 (0.00, 0.07)*
Distensibility, SDS n=3124	-0.07 (-0.10, -0.03)**	-0.04 (-0.08, -0.01)*	-0.05 (-0.08, -0.01)*	-0.05 (-0.09, -0.02)*

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. **P* value <0.05. ***P* value <0.001.

*Values are regression coefficients (95% confidence interval) from regular multivariable linear regression models and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS) and carotid distensibility (SDS) per SDS change in paternal blood pressure. Estimates are from multiple imputed data. Basic models are adjusted for child's age and sex. Confounder model is adjusted for child's age and sex, paternal age, parity, BMI of the father during blood pressure measurement, paternal educational level, paternal ethnicity, maternal folic acid supplementation, maternal smoking and maternal alcohol consumption during pregnancy. Birth model is confounder model additionally adjusted for child's gestational age and weight at birth. Child model is birth model additionally adjusted for offspring breastfeeding status and BMI at time of the measurements.

Table S6. Combined associations of maternal and paternal blood pressure with offspring blood pressure, carotid intima media thickness and carotid distensibility at median 10 years (n=2929)*

Offspring outcomes		Maternal and paternal SBP		
		Basic model	Combined confounder model	Fully adjusted model
SBP, SDS n=2930	Maternal SBP	0.12 (0.09, 0.16)**	0.10 (0.06, 0.14)**	0.09 (0.05, 0.12)**
	Paternal SBP	0.10 (0.07, 0.13)**	0.10 (0.06, 0.13)**	0.11 (0.07, 0.14)**
DBP, SDS n=2930	Maternal SBP	0.07 (0.04, 0.11)**	0.06 (0.02, 0.10)*	0.05 (0.02, 0.09)*
	Paternal SBP	0.03 (-0.01, 0.07)	0.04 (0.01, 0.08)*	0.04 (0.01, 0.08)*
IMT, SDS n=2720	Maternal SBP	-0.02 (-0.06, 0.02)	-0.00 (-0.04, 0.04)	-0.00 (-0.04, 0.04)
	Paternal SBP	0.06 (0.02, 0.10)*	0.06 (0.02, 0.10)*	0.06 (0.02, 0.10)*
Distensibility, SDS n=2583	Maternal SBP	-0.04 (-0.08, -0.01)*	-0.04 (-0.08, 0.00)	-0.03 (-0.07, 0.01)
	Paternal SBP	-0.06 (-0.11, -0.04)**	-0.06 (-0.10, -0.02)*	-0.06 (-0.10, -0.02)*
Offspring outcomes		Maternal and paternal DBP		
		Basic model	Combined confounder model	Fully adjusted model
SBP, SDS n=2930	Maternal DBP	0.11 (0.07, 0.14)**	0.08 (0.04, 0.11)*	0.07 (0.04, 0.11)**
	Paternal DBP	0.07 (0.03, 0.10)**	0.06 (0.02, 0.10)*	0.08 (0.04, 0.11)**
DBP, SDS n=2930	Maternal DBP	0.11 (0.07, 0.14)**	0.09 (0.05, 0.13)**	0.09 (0.05, 0.12)**
	Paternal DBP	0.07 (0.03, 0.11)**	0.09 (0.05, 0.13)**	0.09 (0.06, 0.13)**
IMT, SDS n=2720	Maternal DBP	-0.01 (-0.05, 0.03)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)
	Paternal DBP	0.04 (0.00, 0.08)*	0.04 (-0.00, 0.08)	0.04 (0.00, 0.08)*
Distensibility, SDS n=2583	Maternal DBP	-0.03 (-0.07, 0.01)	-0.02 (-0.06, 0.02)	-0.03 (-0.07, 0.01)
	Paternal DBP	-0.06 (-0.10, -0.02)*	-0.04 (-0.08, 0.00)	-0.04 (-0.08, -0.00)*

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. **P* value <0.05. ***P* value <0.001.

* Values are regression coefficients (95% confidence interval) from regular multivariable linear regression models and reflect the differences in offspring blood pressure (SDS), carotid intima media thickness (SDS) and carotid distensibility (SDS) per SDS change in maternal (early-pregnancy) and paternal blood pressure. Estimates are from multiple imputed data. Basic models are adjusted for child's age and sex. Combined confounder model is adjusted for maternal and paternal confounders, maternal and paternal age, parity, maternal and paternal BMI, maternal and paternal educational level, maternal and paternal ethnicity, maternal folic acid supplementation, maternal smoking and maternal alcohol consumption during pregnancy. Fully adjusted model is the combined model also adjusted for child's gestational age and weight at birth, offspring breastfeeding status and BMI at time of the measurements.

Table S7. Associations of maternal blood pressure with offspring blood pressure, carotid IMT and carotid distensibility at median 10 years in normotensive pregnancies (n=4410)*

Offspring outcomes	Early-pregnancy maternal SBP				Mid-pregnancy maternal SBP				Late-pregnancy maternal SBP			
	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS[†]	0.13 (0.10, 0.17)**	0.11 (0.06, 0.14)**	0.11 (0.08, 0.15)**	0.10 (0.07, 0.13)**	0.16 (0.13, 0.19)**	0.13 (0.10, 0.17)**	0.13 (0.10, 0.16)**	0.12 (0.08, 0.15)**	0.13 (0.10, 0.16)**	0.11 (0.08, 0.14)**	0.11 (0.08, 0.14)**	0.09 (0.06, 0.12)**
DBP, SDS[†]	0.07 (0.04, 0.10)**	0.06 (0.02, 0.10)*	0.06 (0.02, 0.09)*	0.06 (0.02, 0.09)*	0.04 (0.01, 0.07)**	0.06 (0.02, 0.09)**	0.06 (0.03, 0.09)**	0.05 (0.02, 0.09)*	0.04 (0.01, 0.07)**	0.03 (0.00, 0.07)*	0.03 (0.00, 0.06)	0.03 (-0.00, 0.06)
IMT, SDS[‡]	-0.00 (-0.04, 0.03)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0.00 (-0.03, 0.03)	0.02 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.06)	0.02 (-0.01, 0.06)	0.02 (-0.02, 0.05)
Distensibility, SDS[§]	-0.06 (-0.09, 0.02)*	-0.05 (-0.09, -0.02)*	-0.05 (-0.09, 0.02)*	-0.05 (-0.09, 0.01)*	-0.07 (-0.10, -0.04)**	-0.07 (-0.10, 0.03)**	-0.07 (-0.11, -0.03)**	-0.06 (-0.09, 0.09, -0.02)*	-0.05 (-0.08, -0.02)*	-0.04 (-0.08, 0.01)*	-0.04 (-0.08, 0.08, -0.01)*	-0.03 (-0.06, 0.00)
Offspring outcomes	Early-pregnancy maternal DBP				Mid-pregnancy maternal DBP				Late-pregnancy maternal DBP			
	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS[†]	0.12 (0.09, 0.16)**	0.09 (0.06, 0.13)**	0.09 (0.05, 0.13)**	0.09 (0.06, 0.13)**	0.15 (0.12, 0.18)**	0.12 (0.08, 0.15)**	0.11 (0.08, 0.15)**	0.11 (0.08, 0.14)**	0.12 (0.09, 0.15)**	0.09 (0.06, 0.12)**	0.08 (0.05, 0.11)**	0.07 (0.04, 0.10)*
DBP, SDS[†]	0.13 (0.09, 0.16)**	0.11 (0.08, 0.15)**	0.11 (0.07, 0.14)**	0.11 (0.07, 0.14)**	0.13 (0.10, 0.16)**	0.11 (0.08, 0.14)**	0.11 (0.07, 0.14)**	0.10 (0.07, 0.14)**	0.11 (0.08, 0.14)**	0.09 (0.06, 0.12)**	0.09 (0.05, 0.12)**	0.08 (0.05, 0.12)**
IMT, SDS[‡]	-0.00 (-0.04, 0.03)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.03, 0.04)	0.01 (-0.02, 0.05)	0.02 (-0.02, 0.05)	0.02 (-0.02, 0.05)	0.02 (-0.02, 0.05)	0.03 (-0.01, 0.07)	0.03 (-0.00, 0.07)	0.03 (-0.00, 0.06)
Distensibility, SDS[§]	-0.04 (-0.07, 0.00)*	-0.03 (-0.07, 0.01)	-0.04 (-0.07, 0.07, -0.00)*	-0.04 (-0.07, 0.07, 0.00)	-0.07 (-0.10, -0.03)**	-0.06 (-0.09, 0.02)**	-0.06 (-0.09, -0.02)**	-0.06 (-0.09, 0.09, -0.02)*	-0.06 (-0.09, -0.03)**	-0.06 (-0.09, 0.02)**	-0.06 (-0.09, 0.09, -0.02)*	-0.05 (-0.08, 0.02)*

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. *P value <0.05. **P value <0.001.

*Values are regression coefficients (95% confidence interval) that were obtained from regular multivariable linear regression models, and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS) and carotid distensibility (SDS) per SDS change in maternal blood pressure. Estimates are from multiple imputed data. Basic models is adjusted for child's age and sex, and gestational age at the time of blood pressure measurements. Confounder model is basic model additionally adjusted for maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation and smoking and alcohol consumption during pregnancy. Birth model is confounder model additionally adjusted for child's gestational age and weight at birth. Child model is birth model additionally adjusted for offspring breastfeeding status and BMI at time of the measurements. [†] Study population for offspring blood pressure: n=3440 for early-pregnancy, n= 4143 for mid-pregnancy, n=4232 for late-pregnancy. [‡] Study population for offspring IMT: n=3173 for early-pregnancy, n=3836 for mid-pregnancy, n=3919 for late-pregnancy. [§]Study population for offspring distensibility: n=3037 for early-pregnancy, n=3676 for mid-pregnancy, n=3762 for late-pregnancy.

Table S8. Associations of gestational hypertension and preeclampsia with offspring blood pressure, carotid IMT and carotid distensibility at median 10 years excluding small for gestational age below the 3rd percentile (n=4502)*

Offspring outcomes	Normotensive pregnancy	Gestational hypertension				Preeclampsia			
		Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS [†] n=4502	Reference	0.29 (0.14, 0.44)**	0.17 (0.02, 0.32)*	0.17 (0.02, 0.32)*	0.16 (0.02, 0.30)*	0.39 (0.17, 0.62)*	0.29 (0.07, 0.51)*	0.24 (0.02, 0.47)*	0.17 (-0.04, 0.39)
DBP, SDS [†] n=4502	Reference	0.26 (0.11, 0.42)*	0.21 (0.06, 0.37)*	0.21 (0.05, 0.36)*	0.20 (0.05, 0.36)*	0.14 (-0.08, 0.37)	0.08 (-0.14, 0.31)	0.04 (-0.19, 0.27)	0.02 (-0.20, 0.25)
IMT, SDS [‡] n=4171	Reference	-0.03 (-0.19, 0.13)	-0.00 (-0.16, 0.16)	0.01 (-0.15, 0.17)	0.02 (-0.12, 0.19)	0.02 (-0.21, 0.25)	0.02 (-0.21, 0.25)	0.09 (-0.15, 0.32)	0.08 (-0.15, 0.31)
Distensibility, SDS [§] n=4002	Reference	-0.08 (-0.24, 0.08)	-0.03 (-0.20, 0.13)	-0.05 (-0.21, 0.12)	-0.05 (-0.21, 0.11)	-0.16 (-0.39, 0.08)	-0.13 (-0.36, 0.11)	-0.17 (-0.41, 0.07)	-0.14 (-0.37, 0.10)

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. **P* value <0.05. ***P* value <0.001.

*Values are regression coefficients (95% confidence interval) that were obtained from regular multivariable linear regression models, and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS) and carotid distensibility (SDS) for gestational hypertension and preeclampsia. Groups are compared to women with a normotensive pregnancy as reference. Estimates are from multiple imputed data. Basic models are adjusted for child's age and sex. Confounder model is basic model additionally adjusted for maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation and smoking and alcohol consumption during pregnancy. Birth model is confounder model additionally adjusted for child's gestational age and weight at birth. Child model is birth model additionally adjusted for offspring breastfeeding status and BMI at time of the measurements. [†]Study population for offspring blood pressure with 170 cases of gestational hypertension and 76 cases of preeclampsia. [‡]Study population for offspring IMT with 161 cases of gestational hypertension and 74 cases of preeclampsia. [§]Study population for offspring distensibility with 152 cases of gestational hypertension and 69 cases of preeclampsia.

Table S9. Associations of maternal blood pressure with offspring blood pressure, carotid IMT and carotid distensibility at median 10 years excluding small for gestational age below the 3rd percentile (n=4626)*

Offspring outcomes	Early-pregnancy maternal SBP				Mid-pregnancy maternal SBP				Late-pregnancy maternal SBP			
	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS[†]	0.14 (0.11, 0.17)**	0.21 (0.08, 0.15)**	0.11 (0.08, 0.15)**	0.10 (0.07, 0.13)**	0.17 (0.14, 0.19)**	0.14 (0.11, 0.17)**	0.14 (0.11, 0.17)**	0.12 (0.09, 0.15)**	0.15 (0.12, 0.17)**	0.12 (0.09, 0.15)**	0.12 (0.09, 0.15)**	0.10 (0.07, 0.13)**
DBP, SDS[†]	0.07 (0.04, 0.11)**	0.06 (0.03, 0.10)**	0.06 (0.03, 0.10)**	0.06 (0.02, 0.09)*	0.08 (0.05, 0.11)**	0.06 (0.03, 0.09)**	0.06 (0.03, 0.09)**	0.06 (0.03, 0.09)**	0.05 (0.02, 0.08)**	0.04 (0.01, 0.07)**	0.04 (0.01, 0.07)*	0.03 (0.00, 0.07)*
IMT, SDS[‡]	-0.00 (-0.04, 0.03)	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.03, 0.05)	0.01 (-0.02, 0.04)	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.06)	0.02 (-0.01, 0.05)	0.02 (-0.02, 0.05)	0.03 (-0.00, 0.07)	0.03 (-0.00, 0.06)	0.03 (-0.00, 0.06)
Distensibility, SDS[§]	-0.05 (-0.09, 0.01)*	-0.04 (-0.08, -0.01)*	-0.04 (-0.08, -0.01)*	-0.04 (-0.07, -0.01)*	-0.07 (-0.10, -0.04)**	-0.06 (-0.09, -0.03)**	-0.06 (-0.09, -0.03)**	-0.05 (-0.09, -0.02)*	-0.05 (-0.08, -0.02)*	-0.04 (-0.08, -0.01)*	-0.04 (-0.07, -0.01)*	-0.03 (-0.06, 0.00)
Offspring outcomes	Early-pregnancy maternal DBP				Mid-pregnancy maternal DBP				Late-pregnancy maternal DBP			
	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child	Basic	Confounder	Birth	Child
SBP, SDS[†]	0.14 (0.10, 0.17)**	0.10 (0.07, 0.13)**	0.10 (0.06, 0.13)**	0.09 (0.06, 0.13)**	0.16 (0.13, 0.19)**	0.12 (0.09, 0.15)**	0.12 (0.09, 0.15)**	0.11 (0.08, 0.14)**	0.14 (0.11, 0.17)**	0.10 (0.07, 0.13)**	0.10 (0.06, 0.13)**	0.08 (0.05, 0.11)**
DBP, SDS[†]	0.12 (0.09, 0.16)**	0.11 (0.07, 0.14)**	0.11 (0.07, 0.14)**	0.11 (0.07, 0.14)**	0.13 (0.10, 0.16)**	0.11 (0.08, 0.14)**	0.11 (0.08, 0.14)**	0.10 (0.07, 0.14)**	0.11 (0.08, 0.14)**	0.09 (0.06, 0.12)**	0.09 (0.06, 0.12)**	0.08 (0.05, 0.11)**
IMT, SDS[‡]	0.01 (-0.03, 0.04)	0.02 (-0.02, 0.06)	0.03 (-0.01, 0.06)	0.03 (-0.01, 0.06)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.06)	0.02 (-0.01, 0.05)	0.03 (0.00, 0.07)	0.04 (0.01, 0.07)*	0.04 (0.01, 0.07)*
Distensibility, SDS[§]	-0.04 (-0.08, 0.01)*	-0.04 (-0.07, 0.00)*	-0.04 (-0.08, 0.00)*	-0.04 (-0.07, 0.00)*	-0.06 (-0.09, -0.03)**	-0.05 (-0.08, 0.02)*	-0.05 (-0.09, -0.02)*	-0.05 (-0.09, 0.02)*	-0.07 (-0.10, -0.04)**	-0.06 (-0.09, 0.03)**	-0.06 (-0.10, -0.03)**	-0.06 (-0.10, 0.09, -0.02)*

SBP, systolic blood pressure. DBP, diastolic blood pressure. IMT, intima media thickness. *P value <0.05. **P value <0.001.

*Values are regression coefficients (95% confidence interval) that were obtained from regular multivariable linear regression models, and reflect the differences in offspring blood pressure (SDS), carotid IMT (SDS) and carotid distensibility (SDS) per SDS change in maternal blood pressure. Estimates are from multiple imputed data. Basic models is adjusted for child's age and sex, and gestational age at the time of blood pressure measurements. Confounder model is basic model additionally adjusted for maternal age, parity, prepregnancy BMI, educational level, maternal ethnicity, folic acid supplementation and smoking and alcohol consumption during pregnancy. Birth model is confounder model additionally adjusted for child's gestational age and weight at birth. Child model is birth model additionally adjusted for offspring breastfeeding status and BMI at time of the measurements. [†]Study population for offspring blood pressure: n=3616 for early-pregnancy, n=4343 for mid-pregnancy, n=4438 for late-pregnancy. [‡]Study population for offspring IMT: n=3343 for early-pregnancy, n=4030 for mid-pregnancy, n=4118 for late-pregnancy. [§]Study population for offspring distensibility: n=3200 for early-pregnancy, n=3861 for mid-pregnancy, n=3953 for late-pregnancy.

Figure S1. Directed acyclic graph with potential confounders and mediators.

